

PRACE KAZUISTYCZNE

położnictwo

Ballantyne Syndrome (Mirror Syndrome) associated with severe non-immune fetal hydrops – a case report

Zespół Ballantyne'a na tle obrzęku płodu – opis przypadku

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Abstract

Objectives: The aim of the study was to present a case of rapidly progressing non-immune fetal hydrops (NIHF) of unknown etiology in a normal-karyotype fetus, accompanied by severe maternal edema, anemia, and hypoproteinemia. After the differential diagnosis, Ballantyne Syndrome (BS, Mirror Syndrome) was diagnosed.

Material and methods: We present a case of a 31-year-old multipara at 22/24 weeks of pregnancy, presenting severe symptoms of non-immune fetal hydrops: subcutaneous edema, hydrothorax, ascites and placental edema associated with maternal edema, anemia and hypoproteinemia. After cardiovascular, infectious, immune and morphological causes were excluded, amniocentesis was performed and confirmed normal female 46, XX karyotype. Since 22 weeks of pregnancy, increasing maternal edema and anemia were observed. No hematological, cardiac or nephrological causes of this condition were found.

Results: At 24 weeks of pregnancy, intrauterine fetal demise was diagnosed and surgical evacuation (cesarean section) of the fetus was performed. Resolution of maternal edema, anemia, and hypoproteinemia was observed shortly after the delivery.

Conclusions: Based on our findings, it seems safe to conclude that BS may develop in pregnancy complicated by NIHF of unknown origin.

Key words: **Mirror Syndrome / Ballantyne Syndrome / hydrops fetalis / anemia / maternal edema /**

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Streszczenie

Cel pracy: Przedstawienie przypadku zespołu Ballantyne'a (zespołu lustrzanego odbicia) u ciężarnej w ciąży powikłanej szybko postępującym nieimmunologicznym obrzękiem płodu o niewyjaśnionej przyczynie, u płodu z prawidłowym karyotypem, w ciąży zakończonej obumarciem tego płodu w 24 tygodniu.

Materiał i metody: Przedstawiono przypadek 31-letniej wieloródki, u której w 17 tygodniu ciąży rozpoznano u płodu cechy nieimmunologicznego obrzęku: wodobrzusze, wysięk w klatce piersiowej, uogólniony obrzęk tkanki podskórnej i łożyska. Po wykluczeniu przyczyn immunologicznych, infekcyjnych, kardiologicznych oraz anatomicznych, w 17 tygodniu ciąży wykonano amniopunkcję genetyczną i stwierdzono prawidłowy karyotyp żeński. W trakcie kolejnych tygodni ciąży zaobserwowano postępujące zwiększanie się wysięków we wszystkich jamach ciała płodu oraz w tkance podskórnej. Ze względu na zaawasowanie obrzęku, wymiary płodu w 23 tygodniu odpowiadały wymiarom szacowanym na 37 tydzień. W 24 tygodniu doszło do wewnątrzmacicznego obumarcia płodu. Ze względu na wymiary i proporcje obumarłego płodu, ciążę ukończono cięciem cesarskim. W okresie okołoporodowym u matki rozpoznano objawy zespołu Ballantyne'a (zespół lustrzanego odbicia) – narastające obrzęki, oligurię i hypoproteinemię.

Wyniki: Na podstawie przeprowadzonych badań nie udało się postawić jednoznacznej przyczyny występowania obrzęku u płodu.

Wnioski: Wieloczynnikowa etiologia nieimmunologicznego obrzęku płodu w wielu przypadkach nie pozwala na ustalenie jego przyczyny, a co za tym idzie wdrożenia odpowiedniego leczenia. Nieimmunologiczny obrzęk płodu może być przyczyną zespołu Ballantyne'a.

Słowa kluczowe: **obrzęk płodu / wodobrzusze / wysięk / niedokrwistość / zespół lustrzanego odbicia /**

Introduction

Mirror Syndrome (Ballantyne Syndrome, BS) was first described in association with fetal hydrops caused by rhesus-immunization [1]. Nowadays, it is a known fact that BS may occur with non-immune fetal hydrops due to structural and non-structural fetal anomalies: Ebstein's anomaly, Galen's vein aneurysm, placental chorioangiomas, sacrococcygeal teratoma, fetal arrhythmia, or viral infection [2, 3, 4, 5, 6]. Common BS symptoms include maternal edema, anemia, and hypoproteinemia [7]. Care should be taken to distinguish between Ballantyne syndrome and pre-eclampsia. Usually, the concentration of transaminases and platelets remains unaffected in BS, contrary to pre-eclampsia [8].

Objectives

The aim of the study was to present a case of BS in a 31-year-old multipara with severe edema and anemia of unknown origin, mirroring rapidly progressing non-immune fetal hydrops at 22/24 weeks of pregnancy, which resulted in intrauterine fetal demise at 24 weeks of gestation.

Material and methods

A 31-year-old multipara (history of 1 uncomplicated pregnancy, spontaneous term delivery, healthy newborn, normal development) was referred to the Department of Obstetrics and Maternal Diseases at 16 weeks due to signs of non-immune fetal hydrops. An ultrasound examination revealed a single fetus with generalized subcutaneous tissue edema (thickness up to 11 mm), ascites (up to 3.4 mm), placental edema (up to 31 mm), normal amniotic fluid index (AFI), and normal maximum vertical pocket (MVP). No major fetal congenital malformations were detected on ultrasound. Further studies did not reveal the etiology of fetal hydrops – amniotic fluid and serum polymerase chain reaction (PCR) for parvovirus, cytomegalovirus, and toxoplasma were

negative. Amniocentesis confirmed normal female 46,XX karyotype. The above fetal features are presented in Figures 1-4 and major maternal characteristics are shown in Table I. There was no history of chronic diseases, infections, and congenital malformation in the mother.

At 22 weeks, we observed rapid exacerbation of fetal hydrops features. An ultrasound examination was carried out according to the recommendations of the Polish Gynecological Society – Ultrasound Section [9]. We found severe signs of generalized fetal edema: cranial tissue edema (thickness up to 30mm, biparietal diameter (BPD) 112 mm >40wk, >90pc as measured cross-sectionally with edema), abdominal tissue edema (thickness up to 25 mm, abdominal circumference (AC) 333 mm – 37 wk, >90pc, measured in the above mentioned way), abdominal ascites (fluid thickness pocket up to 26 mm), limbs, face and cord edema, hydrothorax (2-3 mm), and pericardial effusion (2 mm). The estimated fetal weight was 3800g when measured cross-sectionally with edematous tissue, and 620 g without edematous tissue. Placental edema was up to 30 mm. Detailed sonographic fetal examination revealed no major congenital malformations. The fetus was given 6 points on the cardiovascular score (CVS) according to Huhta [10]. Doppler ultrasound demonstrated the following: middle cerebral artery pulsatility index (MCA PI) 1.79 (normal) and umbilical artery pulsatility index (UMA PI) 1.31 (upper limit), positive diastolic velocity 11cm/s – presented a trend towards a brain-sparing effect, middle cerebral artery peak systolic velocity (MCA PSV) 34.3 cm/s - <1.5 multiple of median (1.21) according to Mari, non-hyperkinetic flow as present in fetal anemia, laminar umbilical vein (UV) flow, normal ductus venosus (DV) flow with positive A-wave (velocity 12 cm/s), normal fetal movements and borderline hydramnios (AFI 190 mm, MVP 60 mm) [11]. The above mentioned findings are presented in Figures 5-12.

Table 1. Major maternal characteristics in 16wk and 22wk

Parameter	16wk	22wk
TORCH antibodies and PCR	Non-reactive, negative	Non-reactive, negative
Blood type	A positive	A positive
Hemoglobin level (mmol/l)	7,0	5,5, decrease to 4,9
Hematocrite (%)	34	23 – 22
MCV, MCHC, MCH	Normal, not changing	Normal, not changing
PLT (G/L)	280	250, decrease to 137 (normal)
Creatinin (mg/dL)	-	0,75 – 0,65 (normal)
Urea (mg/dL)	-	11,0 – 14,2 (normal)
Total protein (g/dL)	-	5,69, decrease to 4,69 (low)
Albumin level (g/L)	-	26,5 (low)
24h urine protein loss (g)	-	0,25, not significant
Urine excretion (ml)	-	1480
GFR (ml/min)	-	124, decrease to 114 (low)
CRP level (mg/dL)	-	2,31, increase to 57,58 (high)
D-dimer (ng/mL)	-	4730, increase to 9210,0
AspAT, AlAT (mg/dL)	-	13, 22, not changing, (normal)
HIV, HCV antibodies	Non-reactive	Non-reactive

Maternal symptoms were consistent with Mirror Syndrome: face and limb edema, oliguria and anemia. Blood pressure was normal, occasionally at the upper normal range but not requiring pharmacological treatment. There were also severe alterations in the maternal biochemical status (Table 1) and clinical status – increasing lower and upper limb edema, face and abdominal edema and dyspnea, fluid retention (ingested p.o./administered i.v. fluid more than excreted), weight gain of 7 kg between 17-22 weeks, deteriorating anemia (low HGB, HCT) with normal iron level and red-cell parameters. Transaminase (AlAT, AspAT) levels were normal; there was a slight decrease in PLT but the final level was normal. Serum concentration of creatinine and urea was also normal. A 24-hour urine collection revealed non-significant proteinuria, whereas total serum protein, albumin and glomerular filtration rate (GFR) were decreased. There was also an elevated concentration of C-reactive protein (CRP) and D-dimer.

Fetal counselling was conducted by an obstetric and pediatric/neonatal team. The prognosis was established as extremely poor due to massive early fetal hydrops and threatened heart failure. Expectant management was introduced following a consultation with the parents.

At 24 weeks, due to regular uterine contractions and severe fetal bradycardia, after repeated counselling, the cesarean section was performed – for maternal benefit only (indication – fetal bradycardia, severe fetal hydrops). The perinatal outcome was as follows: female newborn-stillbirth at 24 weeks, weight 3090g, placenta was grossly edematous (weight 700 g), Apgar score of 0 at 1 and 5 min., umbilical artery pH 6.82, umbilical vein pH 6.93. The newborn presented generalized skin edema (Figure 13).

Discussion

Ballantyne Syndrome (BS, Mirror Syndrome) is a condition which involves generalized fetal hydrops and associated features – placentomegaly and often polyhydramnios. BS was described in the course of several fetal complications, as indicated above, and often is consistent with preeclampsia [7]. Maternal signs of BS include edema, anemia and hypoproteinemia. Laboratory findings are usually consistent with preeclampsia, except for anemia [8]. In our case study, we described the usual clinical features of BS – deteriorating maternal edema, which was consistent with rapidly progressing fetal hydrops. Maternal laboratory tests were also similar to those in preeclampsia (mild proteinuria). Interestingly, we also demonstrated non-iron deficiency maternal anemia (low HGB and low HCT, probably due to increased maternal serum volume), which was not consistent with fetal anemia. Since repeated non-invasive ultrasound findings did not reveal fetal anemia – median peak systolic velocity for this age was 27.95 cm/s (our measurement 34 cm/s and MCA PSV 1.21 MoM according to Mari), and also for technical reasons (severe cord edema), we decided against performing cordocentesis for fetal anemia check and treatment. The pathogenesis of Mirror Syndrome remains unclear, but the major theories report an imbalance between angiogenic and antiangiogenic factors in maternal serum [12]. Llorba et al., demonstrated resolution of maternal signs of BS caused by bilateral fetal hydrothorax after intrauterine pleuro-amniotic shunt placement. At clinical manifestation, there was an antiangiogenic state similar to the one seen in pre-eclampsia, i.e. increased sFLT-1 and low PlGF concentration, which resolved after fetal treatment and normalized to the values observed in healthy women [13, 14].

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Figure 1. Cranial tissue subcutaneous edema, 17 wk.



Figure 4. Fetal ascites, 17 wk.

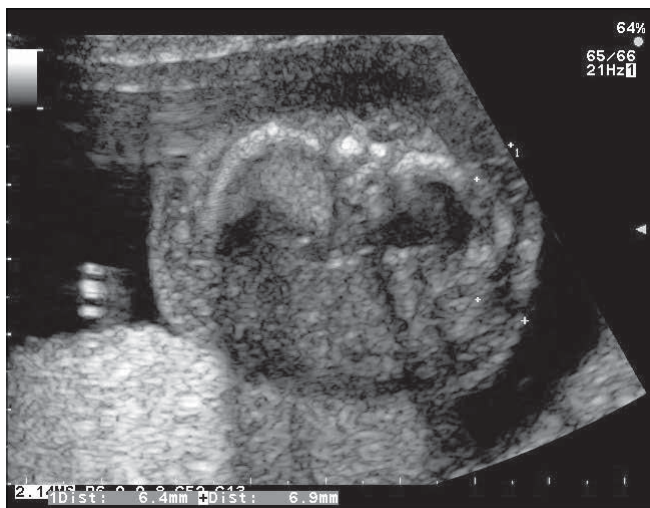


Figure 2. Abdominal tissue subcutaneous edema, 17 wk.

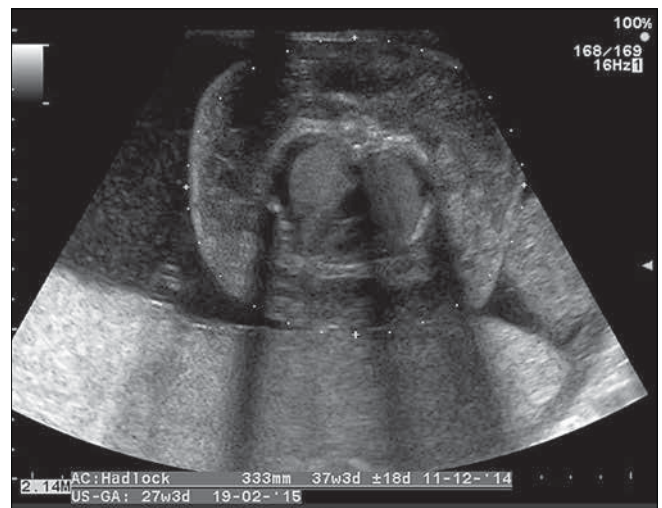


Figure 5. Abdominal subcutaneous tissue edema, 22 wk.

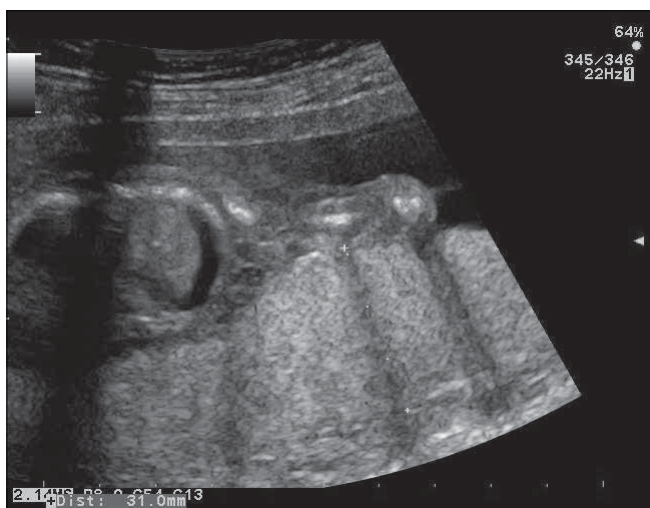


Figure 3. Placental edema, 17 wk.



Figure 6. Cranial tissue subcutaneous edema, 22 wk.

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Figure 7. Ascites and abdominal tissue edema, 22 wk.

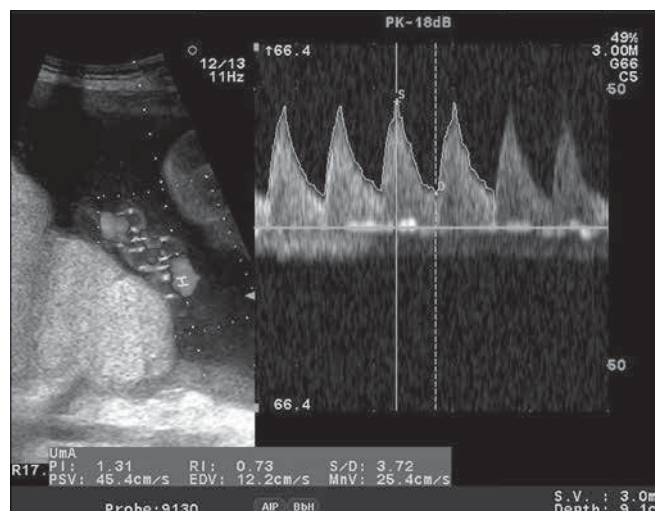


Figure 10. Umbilical artery velocity flow, UMA PI, 22 wk.



Figure 8. Lower limbs skin edema, 22 wk.

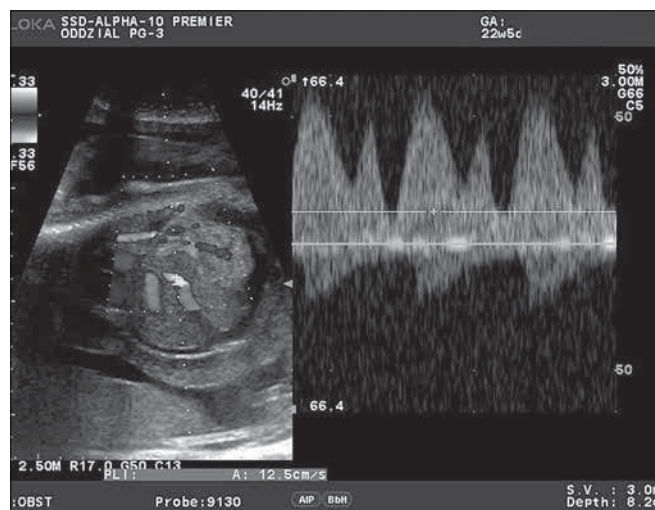


Figure 11. Ductus venosus velocity flow, positive A-wave, 22 wk.

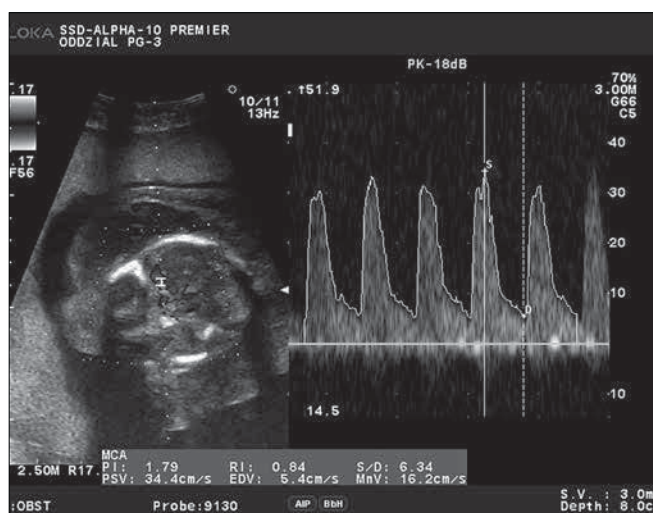


Figure 9. Middle cerebral artery velocity flow, MCA PI and PSV, 22 wk.



Figure 12. Newborn after stillbirth, cesarean section in 24 wk.

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In the largest literature review on the Ballantyne Syndrome – a series of 56 cases – described by Brown et al., the major maternal symptoms included: maternal edema (89.3%) – key symptom in our case, as well as mild anemia and hemodilution (46.4%), mild elevated liver enzymes (19.6%), proteinuria (42.9, oliguria (16.1%) – all present in our case. Other symptoms such as: pulmonary edema (21.4%), elevated blood pressure (60.7%), elevated uric acid and creatinine (25%), headache and visual disturbances (14.3%) and low platelets (7.1%) were not present in our case. Resolution of maternal symptoms after successful fetal treatment or pregnancy end, takes an average of 8-9 days [8]. In our case, 5 days after the caesarean section, we reported resolution of maternal edema. Since the cause of fetal hydrops was unknown, the treatment was not introduced and pregnancy ended with stillbirth at 24 weeks.

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